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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,478	02/15/2007	Vsevolod Ivanovich Kiselev	14940.0004	9362

27890 7590 12/09/2008

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,478	KISELEV ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 74 and 83 have been amended. Claims 1-89 are pending and examined on the merits.

Claim Objections

Claims 1, 5, 31 . 47 and 66 are objected to because of the following informalities: the change in number between section (d) "a hybridoma" and section (e) "the hybridomas" of claim 1; the typographical error of "13" cells in claim 5, rather than "B" cells, the extraneous text in claim 31 before "E coli", the typographical error of "1-ISP70" in claim 47 rather than "HSP70", and the typographical error of "El" oncoprotein in claim 66 section b, rather than "E7" oncoprotein. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low" in claims 1 and 14 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Section 2173 of the M.P.E.P. states

Claims Must Particularly Point Out and Distinctly Claim the Invention

The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent..

In the instant case, the specification does not provide a limiting definition for a "low" immunogenicity which would provide a boundary between that which is "low" versus that which is not low, or "moderate". Thus, a potential infringer would not be able to ascertain when a molecule was large enough not to be considered small, and therefore outside the scope of the claims..

Further, the immunogenic response to any given antigen is a function of the host as well as the antigen. It is unclear if an antigen of "low" immunogenicity is to be defined as having "low" immunogenicity in humans or mammals, or if the antigen of "low" immunogenicity is to be defined as having "low" immunogenicity in the animal to be immunized.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73 and 83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 73 is drawn to a kit comprising at least one reagent that specifically detect E7 oncoprotein. Claim 83 is drawn to a kit comprising at least one reagent that specifically detects Prion protein. The claims thus encompasses a broad genus of "reagents" that would include, binding agents such as antibodies, enzymes, protein ligands or chemical ligands which could be isolated from protein libraries and small molecule chemical libraries. The specification describes only monoclonal antibodies which specifically bind to the prion protein or the E7 protein. This description of a monoclonal antibody fails to adequately describe the genuses encompassed by the claims because each genus comprises structurally unrelated members with respect to monoclonal antibodies. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genuses.

Claims 1-3, 5-16, 18-33, 36-53, 56-65, 67, 74-80, 82, 84-87 and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claims 1, 14, 26, 46, 74, 75, 84 and 85, wherein the animal is a mammal and the hybridoma is produced by a fusion with a non-human immortalized mammalian cell, does not reasonably provide enablement for the method of claims 1, 14, 26, 46, 74, 75, 84 and 85, wherein the animal is not a mammal, or wherein the fusion to provide the hybridoma is with a human immortalized cell, or wherein the screening for specificity is based on a "protein A" assay. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)..

Claims 11, 23, 43 and 63 require the use of an immortalized human cell as an acceptor for a B cell harvested from an immunized animal. The art teaches that chimeric hybridomas made by fusions of human B cells with mouse immortal cells are rare and that most such hybrids, with rare exceptions, tend to be highly unstable due to loss of human chromosomes (Kaplan, 'Monoclonal Human Antibodies', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page18). It would be reasonable to assume that the converse hybridoma, that of a mouse B cell fused to an immortalized human myeloma cell would also be rare and subject to instability due to loss of the human chromosomes. Further, the art teaches that within rodent cells, some combinations of B cells and immortalized cell are less successful than others, for instance Milstein ('Monoclonal Antibodies from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9) and that the importance of the myeloma parental cell line should not be overlooked.. It is reasonable to conclude that not all combinations of activated B cell and immortalized cell will produce a stable chimeric hybridoma secreting antibody. The specification fails to address this unreliability in the

art. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to carry out the claimed methods using an immortalized human cell as the fusion partner for an animal B cell.

Claim 13, 25, 45, 65 and 67 require that the screening of the secreted antibody for specificity is carried out by a "protein A assay". Protein A is known to simply bind to the constant region of an IgG antibody, thus this type of binding would not serve to distinguish the abilities of the antigen-binding portions of the secreted antibody to bind to the specific antigen. One of skill in the art would be subject to undue experimentation is order to screen the secreted antibodies from the hybridomas using a protein A assay for IgG.

Claims 1-3, 5-16, 18-33, 36-53, 56-65, 74-80, 82, 84-87 and 89 are broadly drawn to include the immunization of animals which are not mammals as evidenced by dependent claims 18, 34, 35, 54, 55, 81 and 88. Claims 1-3, 5-16, 18-33, 36-53, 56-65, 74-80, 82, 84-87 and 89 encompass the immunization of "animals" with any antigen of "low" immunogenicity, where said antigen is chemically conjugated to a carrier molecule. Claims 26-33, 36-53, 56-65 and 74 require immunization of animals with E7 oncoprotein that is chemically conjugated to a carrier molecule. Claims 75-80 and 82 require immunization of animals with a prion protein that is chemically conjugated to a carrier molecule. Claims 84 requires immunization of animals with hyaluronic acid chemically conjugated to a carrier molecule. Claims 85-87 and 89 require immunization of animals with matrix metalloprotease 3 chemically conjugated to a carrier molecule. The specification has failed to teach antigens which are of "low immunogenicity" in non-mammalian animals, and has also failed to teach carrier molecules which function in non-mammalian animals to enhance the antigenicity of said antigens with said non-mammalian animals. While it is recognized in the art that nearly all vertebrates make antibodies to a wide range of antigens (Louis DuPasquier, 'Evolution of the Immune System', In: Paul, "Fundamental Immunology", 1993, page 208, second column, first paragraph), most research on the immunization of an animal to produce antibodies for hybridoma formation has been carried out using mammalian animals such as mice, rats and rabbits. Using these mammalian species, much is known about how to enhance the immunogenicity of an antigen by the use of conjugates with carrier proteins (Gorodon L. Ada, 'Vaccines", In: Paul, "Fundamental Immunology", 1993, page 1316, second column under "Conjugates" and the rejections below). Further, the art teaches that

carrier proteins must be "activated" by specific binding groups providing the linkage to the antigen (Seiki et al, U.S. 6, 191, 255, column 19, lines 7-14). It is unknown if the same activated carrier proteins work to enhance immunogenicity to the conjugated antigen in a non-mammalian species, or if different carriers are required, or if the concept of providing a conjugate of the antigen of interest with a carrier protein functions to enhance immunogenicity in the non-mammalian species. One of skill in the art would be subject to undue experimentation in order to carry out the broadly claimed methods in non-mammalian species because it would first be necessary to find carriers to verify if the principle of conjugation to an antigen of low immunogenicity increases the immunogenicity to the antigen.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 6, 8-10, 13-25, 85, 88 and 89 are rejected under 35 U.S.C. 102(b) as being anticipated by Seiki et al (U.S.6,191,255).

Claim 1 is drawn to a method comprising chemically conjugating an antigen of low immunogenicity to a carrier molecule; immunizing an animal with the conjugated antigen; harvesting B cell from the animal; creating hybridomas from the harvested B cells; and screening the antibodies secreted by the hybridomas for specificity to the native antigen of low immunogenicity. Claims 3 and 4 embody the method of claim 1 wherein the animal has an intact immune system. Claims 6 and 8 embody the method of claim 1, wherein the B cells are

harvested from lymph nodes, and spleen, respectively. Claims 9 and 10 embody the method of claim 1 wherein the hybridoma is created using an immortalized mouse cell and a mouse myeloma cell, respectively. Claim 13 embodies the method of claim 1 wherein the specificity of the antibody is screened by ELISA.

Claim 85 is drawn to a method comprising chemically conjugating matrix metalloprotease 3 to a carrier molecule; immunizing an animal with the conjugate; harvesting B cells from the animal; creating hybridomas from the harvested B cells and screening the hybridomas for specificity to the native matrix metalloprotease 3. Claim 88 embodies the method of claim 85 wherein the animal is a mouse. Claim 89 embodies the method of claim 85 wherein the screening using ELISA.

Claims 14-25 are product by process claims, wherein the composition of a monoclonal antibody specific to an antigen of low immunogenicity is carried out by chemical conjugation of the antigen to a carrier molecule and other recited parameters in the method of producing the monoclonal antibody. Section 2113 [R-1] of the MPEP states

> *PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS*
>
> *"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).*

Seiki et al disclose a method of making antibodies to MMP3 comprising immunizing an animal with MM3 conjugated to a carrier molecule (abstract, column 18, lines 27-36 and lines 40-41, column 18, line 63 to column 19, line 18). Seiki et al disclose that mouse myeloma cells are used for cell fusions to produce hybridomas (column 19, line 62 to column 20, line 5). Seiki et al disclose that B cells are isolated from lymph nodes, or spleen (column 20, lines 22-27). Seiki et al disclose immortalized mouse cells including SP2/0-Ag14 for making the fused cells of

the hybridomas (column 19, line 62 to column 20, line 5 and column 34, lines 6-7). Seiki et al disclose that an ELISA was used to isolate the desired MM3 binding antibodies (column 35, lines 7-10) The MM3 binding antibodies of Seiki et al meet the limitations of claims 14-25 because the characteristics of the disclosed antibodies are the same as those claimed.

Claims 1, 3, 4, 8-10, 13-25, 75 and 81-83 are rejected under 35 U.S.C. 102(e) as being anticipated by Cashman et al (U.S. 7,041,807).

Claim 75 is drawn to a method comprising chemically conjugating a Prion protein to a carrier molecule; immunizing an animal with the conjuated antigen; harvesting B cells from the animal; creating hybridomas from the harvested B cells and screening the hybridomas for specificity to the native Prion protein. Claim 81 embodies the method of claim 75 wherein the animal is a mouse. Claim 82 specifies that the screening is done by ELISA.

Claim 83 is drawn to a kit comprising at least one reagent that specifically detects Prion protein and instructions for determining if the subject is at increased risk of developing spongiform encephalopathy.

Cashman et al disclose a method comprising immunizing mice with prion proteins conjugated to KLH, and the isolation of spleenocyte from the immunized mice to make hybridomas, and the screening of said hybridomas by ELISA (column 13, lines 6-42, column 15, lines 58-64) or immunoprecipitation or Western blot (column 17, lines 3-7). Cashman et al disclose fusion of the spleenocyte with immortalized mouse cells (column 13, lines 17-19), and test kits for the diagnosis of prion disease comprising the epitope specific anti-prion antibodies (column 21, line 38 to column 22, line 5). Cashman et al disclose the treatment of prion disease comprising the administration of the anti-prion monoclonal antibodies (column 26, lines 11-36) and pharmaceutical compositions (column 27, line 24 to column 28, line 21). The anti-prion antibodies of Cashman et al meet the limitations of claims 14-25 because the characteristics of the disclosed antibodies are the same as those claimed. Cashman et al meet the limitations of claim 83 with respect to a kit comprising a reagent that specifically detects Prion protein in section (a). Section 2112.01 of the MPEP states:

Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. In re Ngai, F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). See also In re Gulack, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983).

Thus, in the instance case of claim 83, the specific disclosure of the instructions of section (b) in claim 83 does not provide patentable weight to distinguish the claimed kit from the kit of the prior art.

Claims 13-25 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Korth et al (Nature, 1997, Vol. 390, pp. 74-77).

Korth et al disclose the monoclonal antibody of 15B3 which specifically binds to the prion protein PrPsc (page 77, first column, second full paragraph). The disclosure of the antibody meets the limitations of claims 13-25 because the characteristics of the monoclonal antibody are the same as those claimed, and meets the limitations of claim 83 because the recitation of intended use of the kit, or the requirements for instructions for use does not provide patentable weight to distinguish over the prior art monoclonal antibody.

Claims 66, 67, 68, 73 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Mathur et al (American Journal of Reproductive Immunology, 2001, Vol. 46, pp. 280-287).

Claim 66 is drawn to a method comprising obtaining a specimen of cervical epithelial cells and screening said specimen for the presence of the E7 oncoprotein. Claim 67 embodies the method of claim 66 wherein the screening method is selected from a group including an immunofluoresence assay. Claim 68 embodies the method of claim 66 wherein the presence of the E7 oncoprotein is equal to or greater than 0.05 ng/ml.

Mauer et al disclose a method comprising determining the level of E7 protein in a sample of cervical epithelial cells using a monoclonal antibody which binds to E7 and an immunofluorescent assay (pages 283-284 under the heading of "Immunofluorescent Quantification of HPV-E6/E7 and EGF-R in Cervical Epithelial Cells").

Regarding claim 68, Mather et al do not specifically teach that theE7 oncoprotein in the examined tissue samples was equal to greater than 0.05 ng/ml However, the claimed antibodies appears to be the same as the prior art therapeutic agents in terms of binding specificities and cross reactivities, absent a showing of unobvious differences. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim 73 is rejected under 35 U.S.C. 102(e) as being anticipated by Zwerschke et al (WO 2003/080669).

Zwerschke et al disclose antibodies which bind to E7 made by immunizing mice with highly purified E7 protein isolated from E coli, page 9, lines 13-15 and 27-30 and page 12, lines 3-12) which meet the limitations of claims 73 because the recitation of including instructions for determining that the subject is at increased risk of developing CIN is not given patentable weight for the reason set forth above and because the antibodies disclosed by Zwerschke et al are within the scope of at least one reagent that specifically detects E7 oncoprotein.

Claims 14-25, 46, 47, 51-65 and 73 and 74 are rejected under 35 U.S.C. 102(e) as being anticipated by Zatsepina et al (Oncogene, 1997, Vol. 14, pp. 1137-1145). Zatsepina et al disclose monoclonal antibodies, TVGY701 and TVGY703, that specifically bind to the E7 oncoprotein (page 1138 under the heading of "Results"). This disclosure fulfills the embodiments of claim 73 because the intended use of claim 73 is not given patentable weight, nor is the requirement of section b. The disclosure of Zatsepina et al fulfills the requirements of product by process claims 14-25, 46, 47 and 51-65 and 74 because the structure of function of the TVGY701 and TVGY703, are within the scope of the products claimed, and the MPEP states that a product by process claim is characterized by the products rather than the process of making the products..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 3, 4, 8-10, 75, 76 and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cashman et al (U.S. 7,041,807) in view of Lawrence (U.S. 4,859,613).

Claim 76 embodies the method of claim 75 wherein glutaraldehyde is used for the chemical conjugation.

Cashman et al teach the limitations of claims 1, 3, 4, 8-10, 13-25, 75 and 81-83 as set forth above. Cashman et al do not specifically teach the conjugation of the prion proteins to carrier molecules using glutaraldehyde.

Lawrence teaches the use of glutaraldehdye for chemical conjugation of a hapten to the carrier protein of KLH, wherein glutaraldehdye was selected because only monomers of the hapten can be attached to the carrier due to the presence of only one reactive group for the crosslinking reagent, leaving the antigenicity of the hapten intact (column 4, line 59 to column 5, line 27).

It would have been prima facie obvious to use glutaraldehyde to conjugate the prion proteins to the carrier molecules using glutaraldehyde. One of skill in the art would have been

motivated to do so by the teachings of Lawrence et al on the advantage of using glutaraldehyde for conjugations which avoids altering the antigenicity of the hapten.

Claims 1, 3, 4, 6, 8-10, 13, 14, 16-19, 21, 22, 25, 85, 86, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Lawrence (U.S. 4,859,613).

Claim 86 embodies the method of claim 85 wherein the conjugation is performed using glutaraldehyde.

Seiki et al teach the specific embodiments of claims 1, 3, 4, 6, 8-10, 13, 14, 16-19, 21, 22, 25, 85, 88 and 89, for the reasons set forth above. Seiki et al do not specifically teach the conjugation of the MM3 proteins to carrier molecules using glutaraldehyde.

Lawrence teaches the use of glutaraldehdye for chemical conjugation of a hapten to the carrier protein of KLH, wherein glutaraldehdye was selected because only monomers of the hapten can be attached to the carrier protein due to the presence of only one reactive group for the crosslinking reagent, leaving the antigenicity of the hapten intact (column 4, line 59 to column 5, line 27).

It would have been prima facie obvious to use glutaraldehyde to conjugate the MM3 proteins to the carrier molecules using glutaraldehyde. One of skill in the art would have been motivated to do so by the teachings of Lawrence et al on the advantage of using glutaraldehyde for conjugations which avoids altering the antigenicity of the hapten.

Claims 1, 3-6, 8-10, 13-25, 85, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Maurer and Callahan (Methods in Enzymology, 1980, vol. 70A, pp. 49-70).

Claim 5 embodies the method of claim 1 wherein the B cells are harvested from ascites

Seiki et al teach the specific embodiments of claims 1, 3, 4, 6, 8-10, 13, 14, 16-19, 21, 22, 25, 85, 88 and 89, for the reasons set forth above. Seiki et al teach that the antigen is injected intraperitoneally or subcutaneously into the host (column 19, lines 38-48). Seiki et al do not specifically teach that B cells are harvested from ascites.

Maurer and Callahan teach that intraperitoneal injection of antigen into animals results in ascites (page 60, lines 19-20 and page 64, third full paragraph).

It would have been prima facie obvious at the time that the claimed invention was made to use the B cells within the ascitic fluid to make hybridomas. One of skill in the art would have been motivated to do so because the art teaches that ascites can be formed from intraperitoneal injection of antigen and because the ascites fluid produced thereby is easily accessible due to the swelling induced by the fluid accumulation and because the ascites fluid has a high concentration of antibodies and thus B cell producing the antibodies.

Claims 1, 3, 4, 6, 8-10, 12-14, 16-19, 21, 22, 24, 25, 85, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Milstein ('Monoclonal Antibodies from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9).

Claim 12 and claim 24 embodies the methods of claim 1 and claim 14, respectively, wherein the hybridoma is created using an immortal rat cells.

Seikei et al teach immortalized mouse cells for producing hybridomas. Seikei et al do not specifically teach the use of immortal rat cells for producing hybridomas.

Milstein teaches that hybridomas can be made by fusing rat or mouse spleen cells with rat myeloma cells (page 9, Table 1.1).

It would have been prima facie obvious at the time that the claimed invention was made to use rat myeloma cells as the immortalized cell in the method taught by Seiki et al. One of skill in the art would have been motivated to do so by the teachings of Milstein on the successful combination of rat myeloma cells with either mouse or rat spleen cells for the production of hybridomas secreted immunoglobulin.

Claims 1, 3, 4, 8-10, 12-14, 16-18, 21, 22, 24, 25, 75 and 81-83 are rejected under 35 U.S.C. 103(a) as unpatentable over Cashman et al (U.S. 7,041,807) in view of Milstein ('Monoclonal Antibodies from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9).

Claim 12 and claim 24 embodies the methods of claim 1 and claim 14, respectively, wherein the hybridoma is created using an immortal rat cells.

Cashman et al teach the fusion of spleenocyte with immortalized mouse cells for the production of hybridomas (column 13, lines 17-19). Cashman et al do not specifically teach fusion of spleenocyte with immortalized rat cells.

Milstein teaches that hybridomas can be made by fusing rat or mouse spleen cells with rat myeloma cells (page 9, Table 1.1).

It would have been prima facie obvious at the time that the claimed invention was made to use rat myeloma cells as the immortalized cell in the method taught by Cashman et al. One of skill in the art would have been motivated to do so by the teachings of Milstein on the successful combination of rat myeloma cells with either mouse or rat spleen cells for the production of hybridomas secreted immunoglobulin.

Claims 1, 3-5, 8-10, 13-25, 75 and 81-83 are rejected under 35 U.S.C. 103(a) as unpatentable over Cashman et al (U.S. 7,041,807) in view of Maurer and Callahan (Methods in Enzymology, 1980, vol. 70A, pp. 49-70).

Claim 5 and 18 specify that the B cells are harvested from ascites.

Cashman et al teach that the B cells are harvested from the spleen. Cashman et al do not specifically teach that the B cells are harvested from ascites.

Maurer and Callahan teach that intraperitoneal injection of antigen into animals results in ascites (page 60, lines 19-20 and page 64, third full paragraph).

It would have been prima facie obvious at the time that the claimed invention was made to use the B cells within ascitic fluid produced by intraperitoneal injection to make hybridomas. One of skill in the art would have been motivated to do so because the art teaches that ascites can be formed from intraperitoneal injection of antigen and because the ascites fluid produced thereby is easily accessible due to the swelling induced by the fluid accumulation and because the ascites fluid has a high concentration of antibodies and thus B cell producing the antibodies.

Claims 1, 3, 4, 6-10, 13, 14, 16-22, 25, 85, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Burnett et al ('Human

Monoclonal antibodies to Defined Antigens', In: Human Hybridomas and Monoclonal Antibodies, Engleman et al, Ed.s, 1985, page 115)

Claim 7 and claim 21 embody the methods of claims 1 and 14, respectively, wherein the B cells are harvested from the blood.

Seiki et al teach that B cells are harvested from the spleen or lymph nodes (column 20, lines 22-27). Seiki et al do not specifically teach that B cells are harvested from the blood.

Burnett et al teach peripheral blood as a source of B cells after vaccination (pages 115).

It would have been prima facie obvious at the time that the claimed invention was made to use peripheral blood as a source of B cells for the production of hybridomas. One of skill in the art would have been motivated to do so by the teachings of Burnett et al noting this source of antigen-primed lymphocytes and because accessing blood is more convenient that removing the spleen or lymph nodes of an animal.

Claims 1-4, 8-10, 13-18, 21, 22, 25, 75, 80-83 are rejected under 35 U.S.C. 103(a) as unpatentable over Cashman et al (U.S. 7,041,807) in view of Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302).

Claim 2, claim 15, and claim 80 embody the methods of claim 1, claim 14, and claim 75, respectively, wherein the carrier molecule is HSP70.

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to substitute HSP70 for the carrier protein used by Cashman et al. One of skill in the art would have been motivated to do so by the teachings of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response.

Claims 1-4, 6, 8-10, 13-19, 21, 22, 25, 85 and 87-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seiki et al (U.S.6,191,255) in view of Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302).

Claim 2, claim 15, and claim 87 embody the methods of claim 1, claim 14, and claim 85, respectively, wherein the carrier molecule is HSP70

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to substitute HSP70 for the carrier protein used by Seiki et al. One of skill in the art would have been motivated to do so by the teachings of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response.

Claim 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fillit et al (Journal of Experimental Medicine, 1986, Vol. 164, pp. 762-776) in view of Berzofsky et al, ('Antigen-Antibody Interactions and Monoclonal antibodies', In: Fundamental Immunology, W.E. Paul, Ed. 1993, page 458), Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302) and Yokoyama ('Production of Monoclonal Antibodies', In: Current Protocols in Immunology, 1991, Unit 2.5).

Claim 84 is drawn to a method comprising chemically conjugating hyaluronic acid to a carrier molecule; immunizing an animal with the conjugate; harvesting B cells from the animal; creating a hybridoma from the harvested B cells and screening the hybridomas for specificity to native hyaluronic acid.

Fillit et al teach a method for immunizing animals to obtain antiserum to hyaluronic acid comprising immunizing rabbits with formalinized encapsulated streptococci. Fillit et al teach that previous attempts to raise antibodies using hyaluronate conjugated to BSA were unsuccessful (page 762, lines 2-6). Fillit et al did not produce monoclonal antibodies.

Berzofsky et al teaches that monoclonal antibodies can be made reproducible in large quantities offering an advantage over polyclonal antiserum (page 458 under the heading of "Applications of Monoclonal Antibodies").

Yokoyama et al teaches the basic protocol for the production of monoclonal antibodies which includes fusion of spleen cells taken from the immunized animal to create a hybridoma and screening the hybridomas for specificity to the native antigen.

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to conjugate HSP70 to hyaluronate in place of the prior art BSA conjugated to hyaluronate to immunize an animal for the production of monoclonal antibodies One of skill in the art would have been motivated to do so by the teachings of Berzofsky et al on the advantages of having a monoclonal antibody which binds to the antigen of interest over polyclonal antiserum; the teachings of Yokoyama et al on the standard procedure used to produce a monoclonal antibody and the teaching of Lusslow et al on the ability of HSP70 to provide a carrier effect and the induction of a strong antibody response. One of skill in the art would understand that substitution of HSP70 for BSA would have a reasonable expectation of producing an antibody titer in an immunized animal.

Claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 32-36, 39-42, 45-47, 52-56, 59-62, 65, 73, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al (Oncogene, 1997, Vol. 14, pp. 1137-1145) and Yokoyama ('Production of Monoclonal Antibodies', In: Current Protocols in Immunology, 1991, Unit 2.5) Lussow et al (European Journal of Immunology, 1991, Vol. 21, pp. 2297-2302) and Wu et al (U.S. 2004/0086845).

Zatsepina et al teach a method of making the monoclonal antibodies of TVGY701 and TVGY703 which specifically bind the E7 oncoprotein comprising immunizing mice with a purified recombinant E7 protein (page 1138 under "Generation of HPV 16 E7 Monoclonal Antibodies" and page 1144, under the heading of "Antibodies"). Zatsepina et al teach that hybridomas were screened by ELISA, immunoblot and immunoprecipitation. Zatsepina et al do not specifically teach the details of the hybridoma formation. Zatsepina et al do not teach immunization with a HSP70-E7 fusion protein..

Yokoyama teaches the details of forming a hybridoma comprising fusing spleen cells obtained from immunized mice with immortalized mouse myeloma cells.

Wu et al teach that E7 oncoprotein is a weak immunogen (paragraph [0007]).

Lusslow et al teach that HSP70 can substitute for a carrier molecule and induce a strong B cell response without the need for adjuvants as required for other carrier molecules (pages 2299-2300, under section 3.4).

It would have been prima facie obvious to immunize the mice with E7 fused to HSP70. One of skill in the art would be motivated to do so by the teachings of Wu et al on the low immunogenicity of the E7 protein and the teachings of Luslow et al on the strong induction of antibodies using HSP70 as a carrier for antigen. One of skill in the art would be motivated to make the hybridomas by the method of Yokoyama because the method is a standard protocol.

Claims 1-6, 8-10, 13-19, 21, 22, 25, 26, 27, 32-37, 39-42, 45-47, 52-57, 59-62, 65, 73, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 32-36, 39-42, 45-47, 52-56, 59-62, 65, 73, 74 above, and further in view of Seiki et al (U.S.6,191,255).

Claims 6, 19, 37, 57 embody the methods of claims 1, 14, 26 and 46, respectively, wherein the B cells are harvested from lymph nodes.

The combination of Zatsepina et al, Lussow et al, Wu et al and Yokoyama renders obvious the instant methods wherein the B cells are harvested from the spleen. The combination does not teach harvesting B cells from the lymph nodes.

Seiki et al teach that B cells can be harvested from the spleen or the lymph nodes (column 20, lines 22-27).

It would have been prima facie obvious at the time that the invention was made to harvest antigen-primed B cells from the lymph nodes. One of skill in the art would have been motivated to do so by the teachings of Seiki et al which indicate that lymph nodes provide antigen-primed B cells for hybridoma fusions as well as spleen cells

Claims 1-5, 7-10, 13-18, 20-22, 25, 26, 27, 32-36, 38-42, 45-47, 52-56, 58-62, 65, 73, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 32-36, 39-42, 45-47, 52-56, 59-62, 65, 73, 74 above, and further in view of Burnett et al ('Human Monoclonal

antibodies to Defined Antigens', In: Human Hybridomas and Monoclonal Antibodies, Engleman et al, Ed.s, 1985, page 115)

Claims 7, 20, 38, 58 embody the methods of claims 1, 14, 26 and 46, respectively, wherein B cells are harvested from the blood.

Burnett et al teach peripheral blood as a source of B cells after vaccination (pages 115).

It would have been prima facie obvious at the time that the claimed invention was made to use peripheral blood as a source of B cells for the production of hybridomas. One of skill in the art would have been motivated to do so by the teachings of Burnett et al noting this source of antigen-primed lymphocytes and because accessing blood is more convenient that removing the spleen or lymph nodes of an animal.

Claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 31-36, 39-42, 45-47, 51-56, 59-62, 65, 73, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 32-36, 39-42, 45-47, 52-56, 59-62, 65, 73, 74 above, and further in view of Zwerschke et al (WO 2003/080669).

Claims 31 and 51 embody the methods of claims 27 and 47, respectively, wherein the host cell is E coli.

Zatsepina et al teaches the use of recombinant E7 isolated from yeast. Zatsepina et al does not teach the use of recombinant E7 protein isolated from E coli.

Zwerschke et al (WO 2003/080669) teach highly purified E7 protein isolated from E coli, page 9, lines 13-15 and 27-30 and page 12, lines 3-12).

It would have been prima facie obvious at the time that the claimed invention was made to isolate the highly purified E7 protein from E coli.. One of skill in the art would have been motivated to do so because E coli is a common cloning vector and because the expression of the protein in E coli was verified by Zwerschke et al.

Claims 1-5, 8-10, 12-18, 21, 22, 24-27, 32-36, 39-42, 44-47, 52-56, 59-62, 64, 65, 73, 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zatsepina et al, Lussow et al, Wu et al and Yokoyama as applied to claims 1-5, 8-10, 13-18, 21, 22, 25, 26, 27, 32-36, 39-42, 45-47, 52-56, 59-62, 65, 73, 74 above, and further in view of Milstein ('Monoclonal Antibodies

from Hybrid Myelomas', In: Monoclonal Antibodies in Clinical Medicine, McMichael and Favre, Ed.s, 1982, page 9).

Claims 12, 24, 44, 64 embody the methods of claims 1, 14, 26, and 46, respectively, wherein the hybridoma is created using an immortalized rat cell.

Milstein teaches that hybridomas can be made by fusing rat or mouse spleen cells with rat myeloma cells (page 9, Table 1.1).

It would have been prima facie obvious at the time that the claimed invention was made to use rat myeloma cells as the immortalized cell in the method rendered obvious by the combination of Zatsepina et al, Lussow et al, Wu et al and Yokoyama. One of skill in the art would have been motivated to do so by the teachings of Milstein on the successful combination of rat myeloma cells with either mouse or rat spleen cells for the production of hybridomas secreted immunoglobulin.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Karen A Canella/
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